Question 1: Given the profound unmet need for MSD patients, it is our goal to initiate the Phase I/II clinical trial as quickly as possible. The pivotal GLP toxicology study is complete, and the only major barrier to the IND submission is the drug product manufacture and issuance of the COA for inclusion in the IND. To expedite the trial startup, we would like to request to submit the IND prior to completion of the GMP batch, based on the release specification. In this scenario, we would commit to not dosing patients until the IND is updated with the final COA for the clinical batch and at least 30 days have elapsed. Would the Agency be willing to review our IND without the final drug product COA?

FDA response to Question 1: Yes, this is an acceptable plan.

Question 2: Similar to Question 1, to expedite our IND submission and trial startup, we'd like to request to submit the IND with stability data on an engineering batch using a process, materials, and container similar to the GMP drug product batch. We propose to seek IND approval and initiate patient dosing based on the release testing data for the drug product and the stability data on the engineering batch, while the stability testing of the GMP drug product batch is ongoing. The IND will be updated as stability data from the GMP drug product batch becomes available. Does the Agency agree with this plan?

FDA response to Question 2: Yes, this is an acceptable plan.

Question 3: We would like to conduct some of our analytical method qualifications using the toxicology batch made previously at Catalent. Our position is that while the toxicology batch was produced under a different manufacturer and using a slightly different process, enough similarities exist to enable the analytical method work without a meaningful risk of any matrix effects that would impact the reliability or reproducibility of the analytical methods. Similarly, we plan to only conduct product-specific assay qualification on the vector genome titering assay and the mRNA-based in vitro potency assay. The remaining release assays will rely on historical assay qualifications done with similar AAV-based products, and then confirmed for use as fit-for-purpose assays to release AAV9/SUMF1 for this initial Phase I/II study. Does the Agency agree with this plan?

FDA response to Question 3: Yes, this is an acceptable plan.

Question 4: We recognize that we are using a different manufacturer and slightly different manufacturing process for the pivotal toxicology batch and the GMP drug product batch (See Section 5.1 and 5.2). Our position is that the process changes are not likely to adversely affect any critical quality attributes, but that this will need to be assessed through bridging analytical testing. Our approach will be to re-test the toxicology batch by the same methods as the GMP drug product batch, aiming for the GMP drug product batch to meet or exceed the purity of the toxicology batch for the critical quality attributes. This analytical bridging plan is outlined in Section 5.4 (Table 3). In the event that any critical quality attribute in the GMP drug product does not exceed the purity of the toxicology bath, a risk assessment will be

made to address the suitability of the GMP drug product for use in the Phase I/II clinical trial. Does the Agency agree with this analytical bridge testing strategy?

FDA response to Question 4: Yes, this is an acceptable plan.

Question 5: The sponsor proposes to use the mRNA potency assay described in Section 5.5.1 to release drug product for first-in-human clinical studies, which the Agency had indicated would be acceptable during the 2018 pre-IND meeting. Once validated, the investigator and BGTC believe that this potency assay described would be an adequate and reproducible measure of potency for release of Phase III and commercial product. To adequately prepare for the next phases in development of AAV9/SUMF1, the investigator and BGTC request Agency feedback on the plan for potency testing including any guidance on the use of these assays for commercial release of drug product.

FDA response to Question 5: It may be appropriate to continue to use an mRNA assay for later development and commercial release if the mRNA assay has suitable performance characteristics, meaning that the assay would need to have adequate precision, accuracy, linearity, etc. to allow release of drug product against a sufficiently narrow potency acceptance criterion. In addition, the design of the assay would need to incorporate adequate suitability controls and reference materials.

However, an mRNA assay would be insufficient to assure potency if the sequence of the vector is not assured. You state that you will be verifying the sequence of the vector using Sanger sequencing. Sanger sequencing produces a consensus sequence, and therefore it is inadequate to detect sequence variant impurities (for example, point mutations or frameshift mutations that may affect protein translation or function) if such variants are present in a subpopulation of the vector genomes. To adequately assure the sequence of the vector, you would need to use a more sensitive sequencing method such as NGS, and you would need to validate that the method can detect and quantitate sequence variant impurities.

We will be able to provide further feedback about potency assay development after you have submitted an IND that contains detailed information about your potency assurance strategy and potency assays.

[redacted]